Archival Report

Cortical Paired Associative Stimulation Influences Response Inhibition: Cortico-cortical and Cortico-subcortical Networks

Sina Kohl, Ricci Hannah, Lorenzo Rocchi, Camilla L. Nord, John Rothwell, and Valerie Voon

ABSTRACT

BACKGROUND: The ability to stop a suboptimal response is integral to decision making and is commonly impaired across psychiatric disorders. Cortical paired associative stimulation (cPAS) is a form of transcranial magnetic stimulation in which paired pulses can induce plasticity at cortical synapses. Here we used cPAS protocols to target cortico-cortical and cortico-subcortical networks by using different intervals between the paired pulses in an attempt to modify response inhibition.

METHODS: A total of 25 healthy volunteers underwent four cPAS sessions in random order 1 week apart: right inferior frontal cortex (IFC) stimulation preceding right presupplementary motor area (pre-SMA) stimulation by 10 or 4 ms and pre-SMA stimulation preceding IFC stimulation by 10 or 4 ms. Subjects were tested on the stop signal task along with the delay discounting task as control at baseline (randomized across sessions and cPAS protocol) and after each cPAS session.

RESULTS: The stop signal reaction time showed a main effect of cPAS condition when controlling for age ($F_{3,57} = 4.05$, $p = .01$). Younger subjects had greater impairments in response inhibition when the pre-SMA pulse preceded the IFC pulse by 10 ms. In older individuals, response inhibition improved when the IFC pulse preceded the pre-SMA pulse by 4 ms. There were no effects on delay discounting.

CONCLUSIONS: cPAS modified response inhibition through age-dependent long-term potentiation and depression-like plasticity mechanisms via putative cortico-cortical and cortico-subcortical networks. We show for the first time the capacity for cPAS to modify a cognitive process highly relevant to psychiatric disorders.

Keywords: Age, Paired associative stimulation, Plasticity, Response inhibition, Stop signal task, Transcranial magnetic stimulation

https://doi.org/10.1016/j.biopsych.2018.03.009

The ability to stop a suboptimal action—reaching for a cookie, walking into a bar, or perhaps inhibiting an intrusive thought—is integral to our decision-making processes. Impairments in response inhibition, a form of impulsivity, cuts dimensionally across pathological disorders such as substance addiction, eating disorders, obsessive-compulsive disorder, and Parkinson's disease (1,2). Here we used cortical paired associative stimulation (cPAS), a transcranial magnetic stimulation (TMS) protocol often applied to the motor domain, to ask whether cPAS can be applied to the cognitive domain to influence response inhibition.

PAS is a protocol in which repetitive low-frequency paired stimulation can induce changes in excitability by spike timing dependent plasticity–like mechanisms (3). The original PAS protocol (paired peripheral-cortical stimulation) delivered an electrical stimulus to a peripheral nerve just prior to a magnetic stimulus to the contralateral primary motor cortex (3). The repeated pairing or associative process can increase or decrease corticospinal excitability depending on the relative timing of the interaction of stimuli in the cortex (4). These results are explained in terms of spike timing–dependent plasticity from studies at the cellular level where synaptic potentiation (long-term potentiation [LTP]) occurs when an excitatory presynaptic action potential is repeatedly followed by a postsynaptic action potential, whereas synaptic depression (long-term depression [LTD]) occurs when the order of firing is reversed (5). Consistent with spike timing–dependent plasticity features, plasticity induction by PAS tends to be rapid and reversible and persists beyond stimulation. Furthermore, drugs interacting with *N*-methyl-D-aspartate receptors interfere with PAS-induced plasticity, further implying an LTP-like mechanism (3,6).

cPAS is a protocol in which repetitive low-frequency pairs of cortical stimuli (e.g., over parietal and primary motor cortices) can induce changes in cortical excitability. Most studies have focused on the motor domain, given the reliability of the motor-evoked potential (MEP) as an outcome measure. Thus, studies have demonstrated the capacity for cPAS to influence MEP when the conditioning TMS pulse is applied in regions interconnected with primary motor cortex (M1) such as
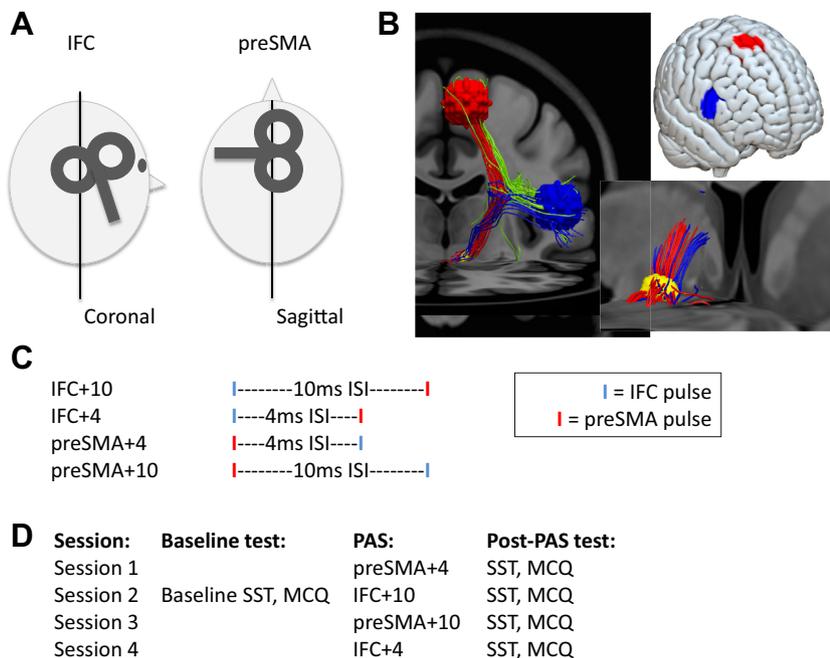
Figure 1. Study design. **(A)** Coil position and orientation over right inferior frontal cortex (IFC) and right presupplementary motor area (pre-SMA). **(B)** Illustration of target areas (in mm): right IFC (blue): x = 48, y = 16, z = 16; right pre-SMA (red): x = 10, y = 10, z = 60 (Montreal Neurological Institute co-ordinates). The tracts displayed are from right IFC and pre-SMA (green), pre-SMA and subthalamic nucleus (red), and right IFC and STN (blue). The bottom right image shows subthalamic nucleus (yellow) with tracts from pre-SMA and right IFC. For tractography analysis, a standardized structural connectome derived from diffusion weighted imaging data of healthy subjects from the Human Connectome Project was used as described elsewhere (47). **(C)** Pulse sequence with interstimulus interval (ISI) of the different stimulation conditions. **(D)** Example illustration of protocol for a subject. Subjects were tested four times 7 days apart. The single baseline test (stop signal task [SST] and Monetary Choice Questionnaire [MCQ]) occurred prior to the paired associative stimulation (PAS), with the order randomized across sessions (here shown in session 2). Only a single baseline test was conducted to avoid excessive repeated testing of the same task. The order of the PAS protocols was randomized across sessions. Subjects were then tested on the SST and MCQ following PAS.

contralateral M1 (7), ventral premotor cortex (8), supplementary motor area (9), and posterior parietal cortex (10). Cortico-subcortical interactions can also be modulated using PAS. A PAS protocol pairing M1 TMS stimulation with subthalamic nucleus (STN) deep brain stimulation enhanced MEPs at 3 and 25 ms, presumed to be related to stimulation of hyperdirect and indirect pathways, respectively (11). Outside motor cortex, a cPAS protocol involving right inferior parietal cortex and dorsolateral prefrontal cortex with a 10-ms interval modulated dorsolateral prefrontal cortex high-frequency oscillatory activity in a direction-specific manner, potentially reflecting LTP- and LTD-like effects (12). Here we proposed to evaluate whether cPAS could influence cognitive networks involved in reactive inhibition and modify a behavioral measure.

Reactive inhibition or stopping involves a frontostriatal network, including right inferior frontal cortex (IFC), pre-supplementary motor area (pre-SMA), caudate, and STN (2,13–15). STN is a nucleus within the indirect pathway receiving significant cortical hyperdirect projections and plays a central role in inhibitory mechanisms. Several theories have been proposed regarding the precise roles and information flow between regions; right IFC has been suggested to be relevant to attentional salience toward the stop signal (16), and pre-SMA to STN output has been suggested to be critical to inhibition (2,17), with effective connectivity suggesting that right IFC precedes pre-SMA temporally (18) (Figure 1B). In the current experiment, we used cPAS to change the effectiveness of the connections in this network and tested whether this had an effect on stopping behavior.
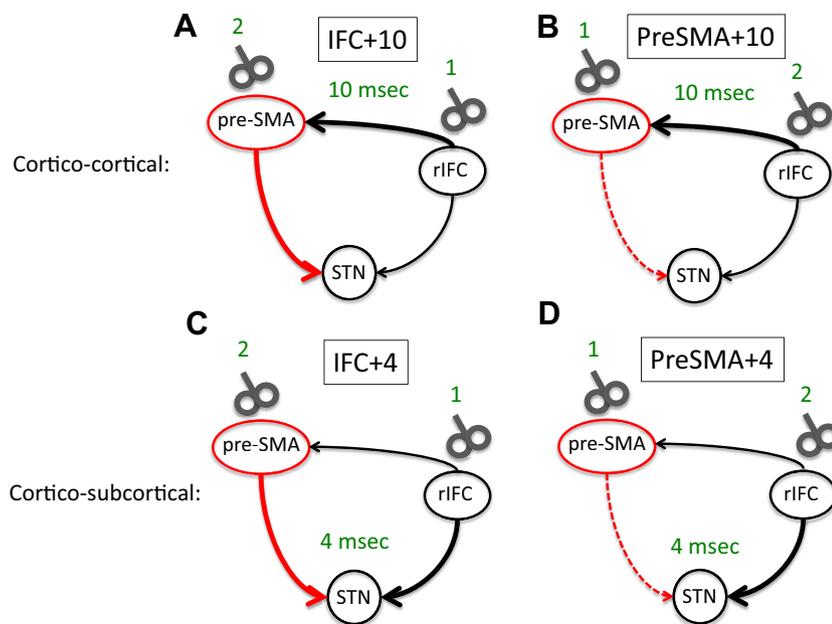
Our design was based on the original M1 PAS model (19). In this, a TMS pulse to M1 activates interneurons in the cortex that receive inputs from the periphery and provide excitation to the corticospinal neurons that project to spinal cord. If peripheral inputs arrive just before the TMS pulse is given, they excite the cortical interneurons and increase the probability that they will discharge in response to the TMS pulse. Repeated pairing of the pulses gradually increases the interneuronal response to TMS, and the result is enhanced activity in the corticospinal output to spinal cord. In our current experiment, we envisaged pre-SMA as equivalent to M1 and pre-SMA output to STN as equivalent to the corticospinal output of M1. Input to pre-SMA from right IFC is equivalent to the peripheral input to M1. Thus, if right IFC inputs are active prior to pre-SMA TMS, then we expect the pre-SMA–STN connection to be strengthened. If right IFC inputs arrive after pre-SMA TMS, then the connection to STN will be weakened.

To allow for an estimated cortico-cortical conduction time of about 8 ms, we stimulated right IFC 10 ms before or after pre-SMA (Figure 1). In hypothesis 1 (Figure 2A), stimulation of right IFC 10 ms before pre-SMA is presumed to facilitate the pre-SMA to STN connections, whereas the opposite timing in hypothesis 2 (Figure 2B) should impair the pre-SMA to STN connection.

As compared with the polysynaptic frontostriatal circuitry involving the prefrontal-striatal-globus pallidus-STN pathway, hyperdirect monosynaptic glutamatergic connections from pre-SMA and IFC to STN have been suggested to provide a rapid signal from cortex to STN relevant to fast reactive processes (20,21). STN single-unit recordings show that successful stops are associated with enhanced neuronal firing following the stop signal, whereas unsuccessful stops or go signals are unchanged from baseline neuronal firing (22,23). The second element of this study, then, asked whether it might be possible to produce subcortical PAS at the level of STN.

Figure 2. Illustration of hypotheses. The illustrations show the hypothesized effects of the paired associative stimulation conditions with the first stimulation pulse (green 1) preceding the second stimulation pulse (green 2) by either 10 ms (presumed cortico-cortical effect) or 4 ms (presumed cortico-subcortical effect). The red indicates the presumed postsynaptic output neuron target. **(A)** Hypothesis 1. Stimulation of right inferior frontal cortex (rIFC) 10 ms before presupplementary motor area (pre-SMA) presumes that the rIFC to pre-SMA input facilitates the pre-SMA to subthalamic nucleus (STN) postsynaptic output activity (in bold red), thereby improving response inhibition via a long-term potentiation-like effect. This effect was not demonstrated. **(B)** Hypothesis 2. Stimulation of pre-SMA 10 ms before rIFC presumes that stimulation of the rIFC to pre-SMA input after pre-SMA stimulation impairs the pre-SMA to STN postsynaptic output activity (in dotted red), thereby impairing response inhibition via a long-term depression-like effect. This effect was demonstrated in younger individuals. **(C)** Hypothesis 3. Stimulation of rIFC 4 ms before pre-SMA is presumed to be too brief for a cortico-cortical effect but presumes that the rIFC input to STN potentiates STN postsynaptic output by strengthening the pre-SMA to STN input (in bold red), thereby improving response inhibition. This hypothesis assumes that input of rIFC to STN precedes input from pre-SMA. This effect was demonstrated in older individuals. **(D)** Hypothesis 4. Stimulation of pre-SMA 4 ms before rIFC presumes the opposite (in dotted red) of hypothesis 3 along with an impairment of response inhibition. This effect was not demonstrated.

The logic of the design is that TMS of right IFC and pre-SMA will activate the hyperdirect pathway to STN. As with cPAS, we hypothesized that if right IFC input arrives first at STN, then it will increase the chance that pre-SMA inputs discharge STN neurons. Repeated pairing at this interval will therefore increase the strength of pre-SMA–STN connections. Reversing the order of the inputs would mean that pre-SMA inputs arrived first and therefore that PAS would strengthen right IFC–STN connections.

Although we do not know the relative conduction times from right IFC–STN and pre-SMA–STN connections, we assume that, given their approximately equal distances, they will also be equal. To allow for the uncertainty, we used timings of +4 ms (right IFC prior to pre-SMA) (hypothesis 3) (Figure 2C) or −4 ms (pre-SMA prior to right IFC) (hypothesis 4) (Figure 2D; see also Figure 1) for our subcortical PAS. Note that given the brevity of the interval, any cortico-cortical effects would differ from those under hypotheses 1 and 2. Thus, assuming an approximate cortico-cortical conduction time of 8 ms, stimulation of right IFC before pre-SMA would mean that cortical input to pre-SMA from right IFC would arrive after pre-SMA TMS and, thus, would reduce the strength of pre-SMA–STN connectivity (as compared with the increase expected if the interval were 10 ms).

As a control outcome measure, we also used a delayed discounting paradigm, a form of impulsivity in which subjects choose between immediate small rewards and larger delayed rewards. Delay discounting is associated with different cortical neural networks from inhibitory function, including dorsolateral and ventromedial prefrontal cortices (24). Thus, we hypothesized effects of cPAS on response inhibition but not on delay discounting.

METHODS AND MATERIALS

Subjects

A total of 30 healthy individuals were enrolled; of these individuals, 5 were excluded (2 fell asleep during some TMS sessions, 1 withdrew, 1 had regular cannabis use, and 1 was missing both baseline and experimental condition data). As a result, 25 individuals over 18 years of age (15 men and 10 women with no major neurological or psychiatric disorders and medication free) were analyzed.

Study Protocol

The study consisted of four experimental sessions of cPAS over right IFC and right pre-SMA (Figure 1D). Prior to the PAS intervention, subjects were tested on one baseline stop signal task (SST) and Monetary Choice Questionnaire (MCQ) to test response inhibition and delay discounting, respectively; the order of the single baseline test was randomized across the four sessions. Subjects underwent four stimulation conditions in a randomized order followed by post-PAS SST and MCQ testing (25). The post-PAS tests were within the 30 minutes during which PAS is presumed to be active (3). The sessions were at least 7 days apart. On the first day, subjects completed the Beck Depression Inventory and an impulsive behavior scale (UPPS-P Impulsive Behavior Scale) (26) and were assessed with the Mini-International Neuropsychiatric Interview.

Subjects were recruited via the University College London healthy volunteer pool. All participants provided written informed consent. Experimental procedures were approved by the University College London Ethics Committee.

TMS Navigation

cPAS TMS was delivered by two Magstim 200^2 machines and two 70-mm figure-of-eight coils (The Magstim Company Ltd., Spring Gardens, Whitland, UK). Coil 1 was positioned over right IFC at a 20° angle to the coronal plane with the handle pointing anteriorly, and coil 2 was positioned over right pre-SMA perpendicular to the midline (Figure 1A). The exact coil positions were guided by neuronavigation (Brainsight; Rogue Research Inc., Montreal, Quebec, Canada). Target sites (Montreal Neurological Institute coordinates [in mm]: right IFC: x = 48, y = 16, z = 16; right pre-SMA: x = 10, y = 10, z = 60) (Figure 1B) were based on a meta-analysis on response inhibition and imaging (27). Pulse intensity was 120% of resting motor threshold (minimum intensity producing low-intensity responses [≥ 50 mV] of the first dorsal interosseous muscle of the left hand in 5 of 10 consecutive trials).

Each cPAS experimental session contained 100 pairs of stimuli at 0.2 Hz (8.3-minute duration). The four experimental conditions differed in the interstimulus interval of the paired pulses; IFC stimulation precedes pre-SMA stimulation by 10 ms (IFC+10) or by 4 ms (IFC+4), and pre-SMA stimulation precedes IFC stimulation by 4 ms (pre-SMA+4) or by 10 ms (pre-SMA+10) (Figures 1C and 2). The cortico-cortical conduction time was presumed to be 8 ms based on facilitatory MEP excitation from other M1 cPAS protocols: ventral premotor (8 ms) (8), M1 (8–10 ms) (7), and parietal (8 ms most consistent; 2–6 ms observed but more variable) (28–30). Other cPAS protocols such as cerebellum to M1 implicate cortico-subcortical connections (31).

Stop Signal Reaction Time Task

Response inhibition was assessed with the SST (Cambridge Cognition, Cambridge, UK). The subject responded to an arrow (go signal), pointing either right or left, by pressing one of two buttons with the right or left index finger. If an audio tone (stop signal) was present, the subject needed to withhold the response. The task uses a staircase model for the stop signal delay by changing the delay by 50 ms depending on stop performance of the previous trial, thereby allowing determination of a stop signal delay at an equal number of successful and unsuccessful stops. The primary outcome measure is the stop signal reaction time (SSRT), which is median reaction time on go trials minus stop signal delay (32). A lower SSRT indicates that less time is required to cancel a motor response and thereby more efficient inhibition.

Monetary Choice Questionnaire

In the MCQ, subjects chose between a small immediate and larger delayed monetary outcome. The primary outcome parameter was the K value, with higher values indicating greater delay discounting.

Data Analysis

We first examined the SSRT and go reaction times for normality of distribution (Shapiro-Wilks test, $p > .05$), sphericity (Mauchly's test, $p > .05$), and outliers (> 3 SD from group mean).

To examine the main hypothesis of effects of the four stimulation conditions on response inhibition, we used a repeated-measures analysis of variance (ANOVA) with the within-subject factor of experimental condition with age as a covariate. We examined the variable of SSRT corrected for baseline (or the difference between post-PAS and pre-PAS SSRT). We show an interaction between experimental condition and age, in keeping with previous observations of an effect of age on PAS plasticity effects (33,34) and on response inhibition (35–38). Because the main effect was significant, we then assessed post hoc comparisons between experimental conditions covaried for age.

Of the 25 subjects, 3 had missing data (each of these subjects was missing a value from one condition: IFC+4, pre-SMA+4, or pre-SMA+10; i.e., 3 missing values from 125). To deal with the missing data, we first conducted the main repeated-measures ANOVA with listwise deletion, thereby including 22 subjects. We then used multiple imputations using regression to provide estimates of the missing data (which draws from a distribution for the missing data over five imputations) and then conducted the repeated-measures ANOVA over all five data sets along with pooling the data.

To further illustrate these findings and the effect of age, we then ran independent t test comparing the difference between post-PAS and pre-PAS SSRT for different experimental conditions between low and high age groups (split by median age = 25 years). To ask which age group was driving the effect, we then ran paired t test comparing post-PAS SSRT versus pre-PAS SSRT separately for low and high age groups. For both analyses, we conducted linewise deletion and multiple imputation analyses. We also assessed the relationship between age and the difference between post-PAS and pre-PAS SSRT using Pearson's correlation coefficient.

We conducted a repeated-measures ANOVA for resting motor threshold. We also conducted repeated-measures ANOVAs for order of experimental condition testing, proportion of successful stops, reaction time on go trials, and the K value of the MCQ comparing experimental conditions as within-subject factors with age as a covariate examining the differences between post-PAS and pre-PAS values.

To understand the effects of baseline SSRT on post-PAS SSRT, we conducted a repeated-measures ANOVA with the within-subject factor of experimental condition with baseline SSRT as a covariate. The significance level was set to .05. All statistical tests were performed using SPSS version 25 (IBM Corp., Armonk, NY).

RESULTS

Demographic Information

The sample consisted of 10 women and 15 men (age [mean ± SD] 26.77 ± 5.54 years; range = 20–39; Beck Depression Inventory: 6.21 ± 5.43; impulsive behavior scale scores: negative urgency 2.91 ± 0.50, premeditation 2.01 ± 0.42, perseverance 1.87 ± 0.47, sensation seeking 2.68 ± 0.25, and positive urgency 2.83 ± 0.45).

TMS Settings

The mean resting motor threshold was 43.42, SD = 8.40 ($p > .05$ across conditions); the mean stimulation conditioning intensity was 52.56, SD = 10.65.
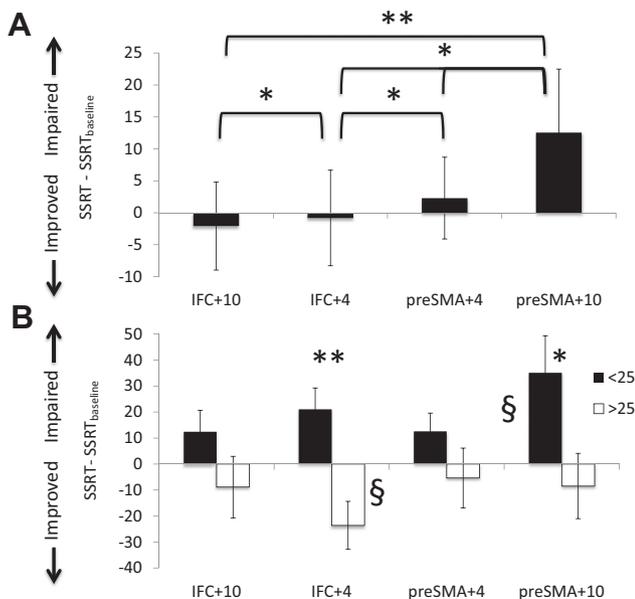
Figure 3. Effect of cortical paired associative stimulation on stop signal reaction time (SSRT). **(A)** The graph represents the repeated-measures analysis of variance comparing the within-subject factor of SSRT for each experimental condition − baseline SSRT (the difference between post- and pre-paired associative stimulation SSRT) covaried with age (main effect: p = .01). The data with linewise deletion of subjects with missing data is shown here. Post hoc analyses covaried with age: *p < .05, **p < .005. **(B)** To further illustrate the effects of age, the graph represents SSRT experimental condition − baseline SSRT separated by the median age (25 years) for each experimental condition. Independent t tests on the median split: *p < .05, **p < .005. Comparing SSRT experimental condition with baseline SSRT for each group showed that the age group differences were driven by the improvement in SSRT in older individuals in inferior frontal cortex (IFC)+4 and the worsening in SSRT in younger individuals in presupplementary motor area (pre-SMA)+10. Paired t tests: §p < .05.

cPAS Effects on SSRT

The data were normally distributed without outliers and fulfilled sphericity assumptions. We first describe the SSRT analysis with listwise deletion of missing data (n = 22) and then with multiple imputations to estimate the missing values (n = 25). We show a main effect of experimental condition ($F_{3,57}$ = 4.05, p = .01) on SSRT (Figure 3A) and an interaction between age and experimental condition ($F_{3,57}$ = 3.51 p = .02) (listwise deletion). These interactions with age are in keeping with the known effect of age on PAS plasticity (33,34) and response inhibition (35,36). Because there was a main effect of condition, we then assessed post hoc comparisons with the co-variate of age; pre-SMA+10 had higher SSRT compared with IFC+10 (p = .014), IFC+4 (p = .001), and pre-SMA+4 (p = .04), and IFC+4 had lower SSRT compared with pre-SMA+4 (p = .007) and IFC+10 (p = .02), with no other differences between conditions (p > .05).

We repeated the analysis with multiple imputations and show similarly a main effect ($Fs_{3,69}$ = 3.51–5.46, ps = .02–.002) and an interaction effect ($Fs_{3,69}$ = 3.18–4.56, ps = .03–.006) across all five iterations. The pooled means were IFC+10 = 3.07, IFC+4 = 2.15, pre-SMA+4 = 4.41, and pre-SMA+10 = 17.71. We repeated the main post hoc analyses; pre-SMA+10

had a higher SSRT than IFC+10 (ps = .04–.005) and IFC+4 had a lower SSRT than pre-SMA+4 (ps = .01–.005) across all five iterations.

To further examine the difference in SSRT with respect to age, we then conducted a median split and compared the two groups (age: mean = 22.43 years, SD = 1.79 and mean = 31.83 years, SD = 3.74). We show differences in stimulation effect for IFC+4 (linewise deletion: t = 3.59, p = .002; pooled: t = 3.45, p = .001) and pre-SMA+10 (linewise deletion: t = 2.28, p = .03; pooled: t = 2.44, p = .02), with younger individuals showing impaired SSRT and older ones showing enhanced SSRT (Figure 3B).

To ask which groups were driving the effect, we compared SSRT experimental condition with baseline separately for the low and high age groups. In the younger age group, pre-SMA+10 showed significantly impaired SSRT versus baseline with multiple imputations (t = −2.20, p = .03), with a trend observed with linewise deletion (t = 2.02, p = .07). In the older age group, the IFC+4 condition showed significantly improved SSRT versus baseline with both multiple imputations (t = 2.55, p = .01) and linewise deletion (t = 2.55, p = .03).

There were also significant correlations between age and cPAS effect in the IFC+4 and pre-SMA+10 conditions (IFC+10: R^2 = .092, p = .142; IFC+4: R^2 = .392, p = .001; pre-SMA+4: R^2 = .054, p = .273; pre-SMA+10: R^2 = .258, p = .013) (Figure 4).

Baseline SSRT, when tested as a covariate, did not have a significant effect on SSRT (main effect: $F_{3,57}$ = 0.25, p = .86; interaction effect: $F_{3,57}$ = 0.52, p = .67).

cPAS Effects on Other SST Parameters

The proportion of inhibition was close to 50% (Table 1) and did not differ across conditions (main effect: $F_{3,66}$ = 0.60, p = .62; interaction effect: $F_{3,66}$ = 0.54, p = .66). The go reaction time did not differ between stimulation conditions (main effect: $F_{3,66}$ = 0.34, p = .79; interaction effect: $F_{3,66}$ = 0.37, p = .74) (Table 1).

Monetary Choice Questionnaire

There were no effects of stimulation condition on delay dis-counting measured using K values in the MCQ (main effect: $F_{3,48}$ = 1.40, p = .25; interaction effect: $F_{3,48}$ = 1.18, p = .33) (Table 1).

DISCUSSION

We investigated for the first time whether cPAS can modulate inhibitory cognitive networks and behavior, varying the timing of cPAS stimulation to probe specific cortico-cortical and cortico-subcortical connections involved in inhibition. We found a sig-nificant effect of cPAS condition on reactive inhibition (SSRT), but, crucially, the influence varies as a function of age. Specif-ically, younger individuals showed a greater impairment in inhi-bition following a cPAS protocol in which the pre-SMA pulse preceded the right IFC pulse by 10 ms (Figure 2B). In contrast, older individuals showed improvements in inhibition when the right IFC pulse preceded the pre-SMA pulse by 4 ms (Figure 2C). Critically, we did not show any effect on delay discounting, an impulsivity measure that implicates different frontostriatal net-works from those targeted by our cPAS protocol (39).
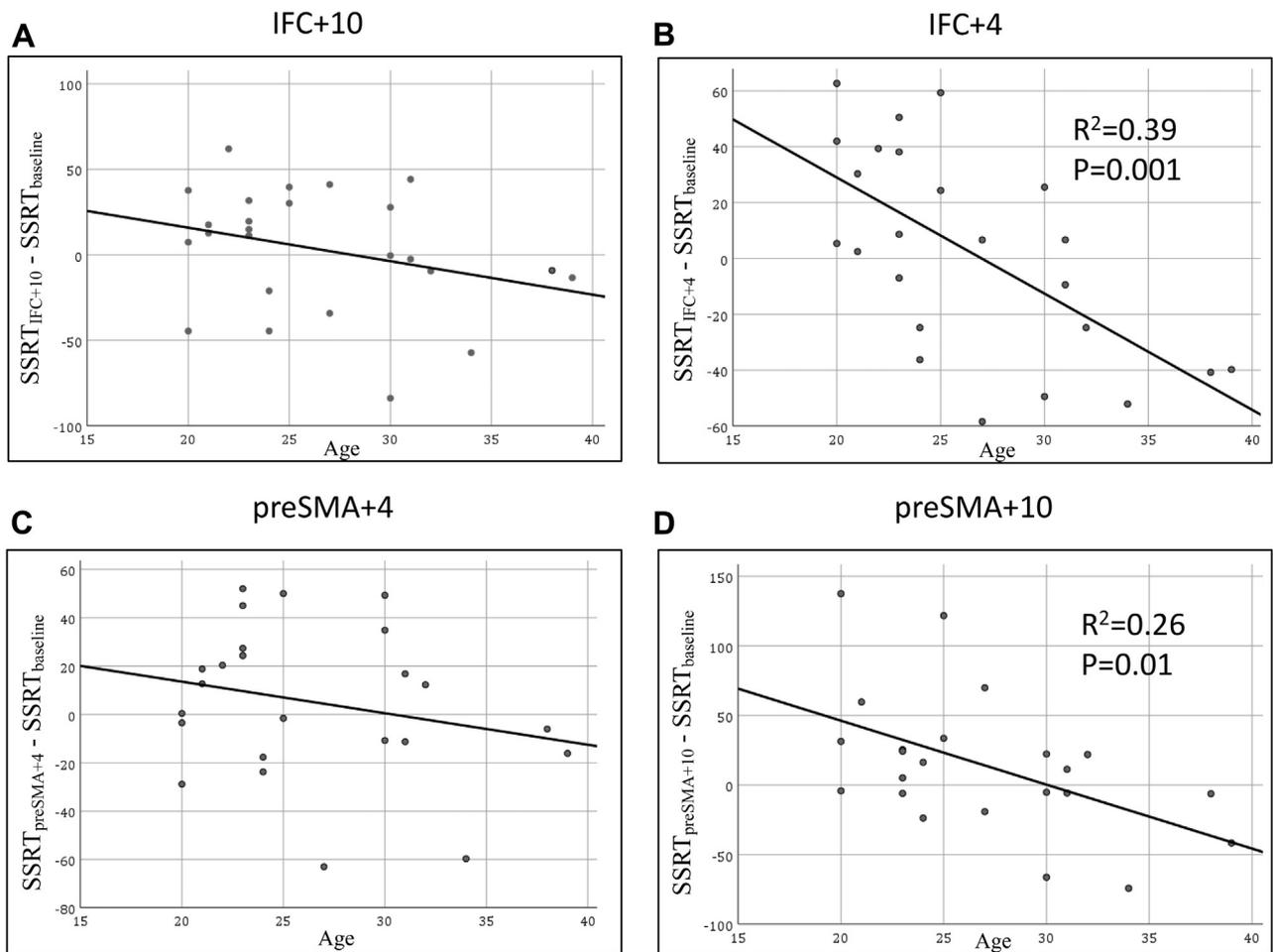
Figure 4. Correlation of age and cortico-cortical paired associative stimulation effect. The correlations show the stop signal reaction time (SSRT), which is experimental condition − baseline, as a function of age: **(A)** inferior frontal cortex (IFC)+10 condition; **(B)** IFC+4 condition; **(C)** presupplementary motor area (pre-SMA)+4 condition; **(D)** pre-SMA+10 condition.

The main effect of cPAS condition, when covaried with age, supported our general hypothesis. The interaction with age has been shown in other PAS protocols in the motor domain, which demonstrate substantial individual differences as a function of age (33,34). We discuss the putative mechanisms of cPAS-induced cortico-subcortical plasticity in the older subgroup, and the mechanisms of the cortico-cortical plasticity effects observed in the younger participants, before speculating as to our age-dependent effects. We emphasize that all of our conclusions related to the anatomical substrates of the observed behavioral phenomena are based on presumed anatomical locations derived from meta-analyses and not from contemporaneous measures in the subjects whose behavior was measured in this study. Thus, we must maintain caution regarding these conclusions, pending a direct test of these substrates via contemporaneous behavioral and functional imaging measures.

Cortico-subcortical Plasticity Induced by cPAS

We hypothesized that stimulation of the right IFC–STN connection 4 ms before the pre-SMA–STN connection would increase the strength of the pre-SMA–STN connection. Right IFC has been suggested to relate to attentional mechanisms

Table 1. SST and MCQ Scores at Baseline and for Each Stimulation Condition

Parameter	Baseline, Mean (SD)	IFC+10, Mean (SD)	IFC+4, Mean (SD)	Pre-SMA+4, Mean (SD)	Pre-SMA+10, Mean (SD)
SST Go RT	347.27 (48.82)	341.79 (49.24)	340.68 (42.74)	342.35 (60.79)	333.50 (34.03)
SST Successful Stop, %	46 (6.12)	48 (6.40)	48 (6.55)	47 (5.51)	47 (8.2)
MCQ, K Value	0.0139 (0.0147)	0.0138 (0.0171)	0.0135 (0.0133)	0.0164 (0.0235)	0.0149 (0.0146)

IFC, inferior frontal cortex; MCQ, Monetary Choice Questionnaire; pre-SMA, presupplementary motor area; RT, reaction time; SST, stop signal task.

(16), while the function of pre-SMA is thought to relate to the stopping process (2,17). Both functional magnetic resonance imaging studies (13) and single-unit recording studies (22,23) implicate STN in inhibition. Functional connectivity of IFC to STN has correlates with SSRT (40). However, the pre-SMA to STN connection seems to be critical for reactive inhibition (17); therefore, right IFC stimulation might prime or facilitate the pre-SMA to STN connection, improving reactive inhibition. This also follows the anatomical conformation of the two regions; IFC is located more ventrally than pre-SMA. Based on rules of ventral internal capsule tract outputs, ventral tracts will exit earlier than dorsal tracts, suggesting that stimulation of right IFC tracts to STN should precede that of pre-SMA tracts to STN (41). Note that with this timing there is the possibility of some cortico-cortical interaction. However, as explained in the introductory paragraphs, if this occurred, it would be the opposite of the subcortical interaction and at +4 ms would be expected to reduce the effectiveness of the pre-SMA input to STN. Given that reactive inhibition improves, we conclude that the cortico-cortical effect is weaker than the subcortical effect, at least in older subjects (see below), resulting in a stronger pre-SMA input to STN.

Here we presume an effect at the level of STN, which has been particularly implicated in reactive inhibition. Equally, an effect could be observed at the level of striatum; however, if inhibitory caudate output of both the indirect and direct pathways were enhanced, these effects might cancel out and not necessarily change thalamocortical output.

Cortico-cortical Plasticity Induced by cPAS

We also hypothesized that cPAS might modulate cortico-cortical plasticity by improving response inhibition when right IFC stimulation preceded pre-SMA stimulation by 10 ms. Our results did not support this hypothesis. However, our findings did support the hypothesis of impairment in response inhibition when the right IFC pulse occurred 10 ms after the pre-SMA pulse, particularly in younger participants. Thus, stimulation of IFC to pre-SMA input after stimulation of pre-SMA appears to impair the primary postsynaptic pre-SMA to STN output (hypothesis 2), suggestive of an LTD-like effect.

Our failure to find an improvement in response inhibition with IFC+10 is unexpected, but it may simply be that there is an asymmetry in the effectiveness of the cPAS protocol such that the inhibitory interactions are stronger than the facilitatory ones. A similar asymmetry was seen in the original M1 PAS in which the facilitatory effect was larger and more reliable than the inhibitory effect (3). We have not discussed plasticity at the IFC–pre-SMA connection, which is also theoretically plausible.

Age Dependence of Effects

We observe a strong interaction effect of age with our effect of interest on cPAS condition. Most simply, this effect may relate to general age-related differences in response inhibition. Younger participants, who show faster SSRTs, may show a ceiling effect, being receptive only to potential impairments following intervention; the slower SSRTs of older participants might be receptive to possible improvements but show a floor effect to potential impairments. We do not observe an effect of

baseline interindividual SSRT on the effects of cPAS condition, suggesting that this explanation of a baseline effect by itself is insufficient; however, an interaction between baseline and age remains plausible. SSRT declines with much older age (38 years), but in a large online study demonstrating a linear age-related impairment in SSRT, the impairment started between the ages of 18–29 and 30–39 years (38). Furthermore, young adults (20–42 years), as compared with adolescents (10–17 years), showed greater right IFC activation during successful inhibition (36), a finding that might explain why right IFC stimulation preceding pre-SMA might facilitate inhibition in our older participants.

An alternative explanation might lie in the relationship between neurodevelopmental processes and cPAS. Myelination of the prefrontal cortex and synaptic pruning of unnecessary prefrontal synaptic connections, both mechanisms underlying efficacy of communication, are understood to persist until 25 years of age (42,43). In the case of synaptic pruning, greater aberrant and excessive synaptic inputs or outputs in younger individuals might impair the precision of the signal from IFC to the same STN neurons targeted by pre-SMA; thus, the potentiating effects of cPAS (LTP) might not occur to their full extent, and the inhibitory effects (LTD) might appear to be more prominent as observed. The effects of myelination and synaptic pruning on conduction times might have an effect on younger individuals but is less likely to have a marked effect on the age range tested.

Age effects on cortical plasticity have been demonstrated (44). Practice-dependent plasticity (45) and modulation of task-specific activity in motor networks show age-related effects (46). Age effects have also been observed with PAS involving median nerve stimulation and MEP in individuals over 60 years old and in postmenopausal women (33,34), although they may also be apparent in individuals over 31 years old (34), suggesting impaired LTP processes with aging. Mechanisms postulated to underlie these age-related effects on plasticity include changes in neurochemistry, neurotrophic factors, and excitability of cortical inhibitory circuits (33,34).

Future Directions and Limitations

Future studies should delineate the neural mechanisms of cPAS and its relationship with age. Baseline effects could be further tested using an interval unlikely to have a PAS effect. Testing other intervals is also indicated.

Conclusions

We show for the first time that cPAS can influence a cognitive process outside of the motor domain. The effect appears to be specific to inhibitory networks on response inhibition with no effect on delay discounting, an impulsivity measure that implicates different networks, implying network target specificity. cPAS appears to influence cortico-cortical and cortico-subcortical pathways, possibly via LTD- and LTP-like processes, but is critically dependent on age. Nevertheless, given that response inhibition is impaired dimensionally across psychiatric disorders, this represents a novel means of noninvasive neuromodulation of an important cognitive process. In particular, the capacity to improve SSRT via priming pre-SMA to STN function in older individuals is potentially a critical therapeutic modality.

ARTICLE INFORMATION

From the Department of Psychiatry (SK, CLN, VV) and Behavioural and Clinical Neurosciences Institute (VV), University of Cambridge, and Cambridgeshire and Peterborough National Health Service Foundation Trust (VV), Addenbrookes Hospital, Cambridge, and Sobell Department of Motor Neuroscience and Movement Disorders (RH, LR, JR), University College London Institute of Neurology, London, United Kingdom; and Department of Psychiatry and Psychotherapy (SK), University of Cologne, Cologne, Germany.

Address correspondence to Valerie Voon, M.D., Ph.D., Department of Psychiatry, University of Cambridge, Cambridge CB2 0QQ, United Kingdom; E-mail: voonval@gmail.com.

Received Jan 17, 2018; revised Mar 22, 2018; accepted Mar 23, 2018.

REFERENCES

1. Dalley JW, Everitt BJ, Robbins TW (2011): Impulsivity, compulsivity, and top-down cognitive control. Neuron 69:680–694.
2. Aron AR (2011): From reactive to proactive and selective control: Developing a richer model for stopping inappropriate responses. Biol Psychiatry 69:e55–e68.
3. Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J (2000): Induction of plasticity in the human motor cortex by paired associative stimulation. Brain 123(Pt 3):572–584.
4. Wolters A, Sandbrink F, Schlottmann A, Kunesch E, Stefan K, Cohen LG, et al. (2003): A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex. J Neurophysiol 89:2339–2345.
5. Katz LC, Shatz CJ (1996): Synaptic activity and the construction of cortical circuits. Science 274:1133–1138.
6. McKay DR, Ridding MC, Thompson PD, Miles TS (2002): Induction of persistent changes in the organisation of the human motor cortex. Exp Brain Res 143:342–349.
7. Rizzo V, Siebner HS, Morgante F, Mastroeni C, Girlanda P, Quartarone A (2009): Paired associative stimulation of left and right human motor cortex shapes interhemispheric motor inhibition based on a Hebbian mechanism. Cereb Cortex 19:907–915.
8. Buch ER, Johnen VM, Nelissen N, O'Shea J, Rushworth MF (2011): Noninvasive associative plasticity induction in a corticocortical pathway of the human brain. J Neurosci 31:17669–17679.
9. Arai N, Muller-Dahlhaus F, Murakami T, Bliem B, Lu MK, Ugawa Y, et al. (2011): State-dependent and timing-dependent bidirectional associative plasticity in the human SMA-M1 network. J Neurosci 31:15376–15383.
10. Veniero D, Ponzo V, Koch G (2013): Paired associative stimulation enforces the communication between interconnected areas. J Neurosci 33:13773–13783.
11. Udupa K, Bahl N, Ni Z, Gunraj C, Mazzella F, Moro E, et al. (2016): Cortical plasticity induction by pairing subthalamic nucleus deep-brain stimulation and primary motor cortical transcranial magnetic stimulation in Parkinson's disease. J Neurosci 36:396–404.
12. Casula EP, Pellicciari MC, Picazio S, Caltagirone C, Koch G (2016): Spike-timing-dependent plasticity in the human dorso-lateral prefrontal cortex. NeuroImage 143:204–213.
13. Aron AR, Poldrack RA (2006): Cortical and subcortical contributions to Stop signal response inhibition: Role of the subthalamic nucleus. J Neurosci 26:2424–2433.
14. Aron AR, Herz DM, Brown P, Forstmann BU, Zaghloul K (2016): Frontosubthalamic circuits for control of action and cognition. J Neurosci 36:11489–11495.
15. Watanabe T, Hanajima R, Shirota Y, Tsutsumi R, Shimizu T, Hayashi T, et al. (2015): Effects of rTMS of pre-supplementary motor area on fronto basal ganglia network activity during stop-signal task. J Neurosci 35:4813–4823.
16. Cai W, Chen T, Ide JS, Li CR, Menon V (2017): Dissociable fronto-operculum-insula control signals for anticipation and detection of inhibitory sensory cue. Cereb Cortex 27:4073–4082.
17. Obeso I, Wilkinson L, Teo JT, Talelli P, Rothwell JC, Jahanshahi M (2017): Theta burst magnetic stimulation over the pre-supplementary motor area improves motor inhibition. Brain Stimul 10:944–951.
18. Duann JR, Ide JS, Luo X, Li CS (2009): Functional connectivity delineates distinct roles of the inferior frontal cortex and presupplementary motor area in stop signal inhibition. J Neurosci 29:10171–10179.
19. Weise D, Mann J, Ridding M, Eskandar K, Huss M, Rumpf JJ, et al. (2013): Microcircuit mechanisms involved in paired associative stimulation-induced depression of corticospinal excitability. J Physiol 591:4903–4920.
20. Haynes WI, Haber SN (2013): The organization of prefrontal-subthalamic inputs in primates provides an anatomical substrate for both functional specificity and integration: Implications for basal ganglia models and deep brain stimulation. J Neurosci 33:4804–4814.
21. Nambu A, Tokuno H, Takada M (2002): Functional significance of the cortico-subthalamo-pallidal "hyperdirect" pathway. Neurosci Res 43:111–117.
22. Bastin J, Polosan M, Benis D, Goetz L, Bhattacharjee M, Piallat B, et al. (2014): Inhibitory control and error monitoring by human subthalamic neurons. Transl Psychiatry 4:e439.
23. Benis D, David O, Piallat B, Kibleur A, Goetz L, Bhattacharjee M, et al. (2016): Response inhibition rapidly increases single-neuron responses in the subthalamic nucleus of patients with Parkinson's disease. Cortex 84:111–123.
24. Voon V, Dalley JW (2016): Translatable and back-translatable measurement of impulsivity and compulsivity: Convergent and divergent processes. Curr Top Behav Neurosci 28:53–91.
25. Kirby KN, Petry NM, Bickel WK (1999): Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. J Exp Psychol Gen 128:78–87.
26. Cyders MA, Smith GT (2008): Emotion-based dispositions to rash action: Positive and negative urgency. Psychol Bull 134:807–828.
27. Cieslik EC, Mueller VI, Eickhoff CR, Langner R, Eickhoff SB (2015): Three key regions for supervisory attentional control: Evidence from neuroimaging meta-analyses. Neurosci Biobehav Rev 48:22–34.
28. Karabanov AN, Chao CC, Paine R, Hallett M (2013): Mapping different intra-hemispheric parietal-motor networks using twin coil TMS. Brain Stimul 6:384–389.
29. Chao CC, Karabanov AN, Paine R, Carolina de Campos A, Kukke SN, Wu T, et al. (2015): Induction of motor associative plasticity in the posterior parietal cortex-primary motor network. Cereb Cortex 25:365–373.
30. Koch G, Fernandez Del Olmo M, Cheeran B, Ruge D, Schippling S, Caltagirone C, et al. (2007): Focal stimulation of the posterior parietal cortex increases the excitability of the ipsilateral motor cortex. J Neurosci 27:6815–6822.
31. Lu MK, Tsai CH, Ziemann U (2012): Cerebellum to motor cortex paired associative stimulation induces bidirectional STDP-like plasticity in human motor cortex. Front Hum Neurosci 6:260.
32. Logan GD, Cowan WB, Davis KA (1984): On the ability to inhibit simple and choice reaction time responses: A model and a method. J Exp Psychol Hum Percept Perform 10:276–291.
33. Fathi D, Ueki Y, Mima T, Koganemaru S, Nagamine T, Tawfik A, et al. (2010): Effects of aging on the human motor cortical plasticity studied by paired associative stimulation. Clin Neurophysiol 121:90–93.
34. Muller-Dahlhaus JF, Orekhov Y, Liu Y, Ziemann U (2008): Interindividual variability and age-dependency of motor cortical plasticity induced by paired associative stimulation. Exp Brain Res 187:467–475.
35. Velanova K, Wheeler ME, Luna B (2008): Maturational changes in anterior cingulate and frontoparietal recruitment support the development of error processing and inhibitory control. Cereb Cortex 18:2505–2522.
36. Rubia K, Smith AB, Taylor E, Brammer M (2007): Linear age-correlated functional development of right inferior fronto-striato-cerebellar

networks during response inhibition and anterior cingulate during error-related processes. Hum Brain Mapp 28:1163–1177.

37. Bedard AC, Nichols S, Barbosa JA, Schachar R, Logan GD, Tannock R (2002): The development of selective inhibitory control across the life span. Dev Neuropsychol 21:93–111.

38. Smittenaar P, Rutledge RB, Zeidman P, Adams RA, Brown H, Lewis G, et al. (2015): Proactive and reactive response inhibition across the lifespan. PLoS One 10:e0140383.

39. Frost R, McNaughton N (2017): The neural basis of delay discounting: A review and preliminary model. Neurosci Biobehav Rev 79:48–65.

40. Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA (2007): Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. J Neurosci 27:3743–3752.

41. Lehman JF, Greenberg BD, McIntyre CC, Rasmussen SA, Haber SN (2011): Rules ventral prefrontal cortical axons use to reach their targets: Implications for diffusion tensor imaging tractography and deep brain stimulation for psychiatric illness. J Neurosci 31: 10392–10402.

42. Casey BJ, Jones RM, Hare TA (2008): The adolescent brain. Ann N Y Acad Sci 1124:111–126.

43. Sousa SS, Amaro E Jr, Crego A, Goncalves ÓF, Sampaio A (2018): Developmental trajectory of the prefrontal cortex: A systematic review of diffusion tensor imaging studies. Brain Imaging Behav 12:1197–1210.

44. Hanajima R, Tanaka N, Tsutsumi R, Enomoto H, Abe M, Nakamura K, et al. (2017): The effect of age on the homotopic motor cortical long-term potentiation-like effect induced by quadripulse stimulation. Exp Brain Res 235:2103–2108.

45. Sawaki L, Yaseen Z, Kopylev L, Cohen LG (2003): Age-dependent changes in the ability to encode a novel elementary motor memory. Ann Neurol 53:521–524.

46. Ward NS, Swayne OB, Newton JM (2008): Age-dependent changes in the neural correlates of force modulation: An fMRI study. Neurobiol Aging 29:1434–1446.

47. Horn A, Reich M, Vorwerk J, Li N, Wenzel G, Fang Q, et al. (2017): Connectivity predicts deep brain stimulation outcome in Parkinson disease. Ann Neurol 82:67–78.